enabling. It is respectfully submitted, however, that the Examiner has failed to set forth a prima facie case for lack of enablement.

The predecessor to the Federal Circuit has stated:

> "[A] specification disclosure which contains a teaching of the manner and process of making and using the invention in terms which correspond in scope to those used in describing and defining the subject matter sought to be patented must be taken as in compliance with the enabling requirement of the first paragraph of section 112 unless there is reason to doubt the objective truth of the statements contained therein which must be relied on for enabling support."

In re Brana, 51 F.3d 1560, 1566 (Fed. Cir. 1995), citing, In re Marzocchi, 439 F.2d 220, 223 (C.C.P.A. 1971)(emphasis supplied). Thus, the PTO has the initial burden of challenging a presumptively correct assertion of utility in the disclosure. Brana, 51 F.3d at 1566. Only after the PTO provides evidence showing that one of ordinary skill in the art would reasonably doubt the asserted utility does the burden shift to the applicant to provide rebuttal evidence sufficient to convince such a person of the invention's asserted utility. Id. Here, as in the Brana case, the Examiner has issued a rejection standing on the requirements of § 112, paragraph 1, although the rejection is seemingly based on a utility issue, i.e. whether Applicant's invention has utility to regulate NO production in a mammal subject based on *in vitro* experimental evidence.

Pursuant to the new utility guidelines, in order for a rejection for lack of utility to be proper, the Examiner must make a prima facie showing that the claimed invention has no utility. See 1170 O.G. 483 (January 31, 1995). The prima facie showing must include: 1) a well reasoned statement by the Examiner that clearly sets forth the reasoning used in reaching his or her conclusions; 2) support for factual findings relied upon by the Examiner in reaching his or her conclusions; and 3) support for conclusions of the Examiner that evidence provided by the applicant to support an asserted utility would not be considered persuasive to a person of ordinary skill in the art. Id. The evidence provided by the Examiner must include whenever possible documentary evidence that supports the factual basis of the prima facie showing of no utility. Id.

The Examiner first asserts that claims 1-15 are not enabled on the basis that, "[d]osages which are critical or essential to the practice of the invention but not included in the claims is not enabled by the disclosure." (Office Action p. 2). It is the Examiner's position that the specification is not enabling for the claimed invention "because neither dosages of the various 'drugs' or inhibitors, which belong to the classes of peptides, oligopeptides or proteins are given in the generic disclosure of the invention." (Office Action, p. 2). The Examiner further argues that there are no "examples of dosages of these agents given to any mammal which

effects a measurable response which might be interpreted as NO production decrease or increase from which one skilled in the art might extrapolate to all mammals." (Office Action, p. 2). However, as set forth above, it is not Applicants' burden to provide such evidence. Instead, only after the Examiner meets the initial burden of demonstrating why one of ordinary skill in the art would doubt the truth of Applicant's presumptively enabling disclosure does the burden switch to Applicant to provide evidence of enablement. It is submitted that the Examiner's unsupported statement of lack of enablement without documentary evidence or scientific support does not meet this initial burden.

Furthermore, the Examiner's assertion that there are no examples of dosages of the various drugs or inhibitors of the invention is not correct. Page 36 of the specification provides extensive dosing guidelines pertaining to the administration of the substrate of this invention. Specifically, the specification states that suitable ranges for IV administration are typically about 20-500 μg of active compound per kilogram of body weight. This latter dosing range is now set forth in claims 1 and 10 from which claims 2-9 and 11-15 ultimately depend.

Moreover, pages 43-44 of the specification provide the inhibitory constants and enzyme kinetic constants that were determined for the oligopeptide substrates and inhibitors of the claimed invention. These constants are similar to those

reported for arginine and arginine-based inhibitors. Persons skilled in the art of pharmacology would be readily able to use these physical constants for the conversions of arginine-containing peptides to nitric oxide by nNOS-II for extrapolating the doses for use in mammals.

The Examiner has provided no evidence as to why those of ordinary skill in the art would not be able to reasonably correlate Applicant's specifically disclosed dosages and inhibitory and enzyme kinetic constants to determine a suitable dose for administration to mammals. Here, the specification provides a reasonable amount of guidance to those skilled in the art of pharmaceutics to determine a suitable dose of the peptide, oligopeptide, or protein for practicing the claimed invention within the dosing ranges set forth in claims 1-15 and using these inhibitory and enzyme kinetic constants without an undue amount of experimentation.

The Examiner also states that Applicants' examples of additions of certain peptides and oligopeptides to a purified NO synthase in a test tube "is not an art accepted model, the results of which may be readily extrapolated to an *in vivo* system" and that "no evidence is of record that such a system which can correlate this *in vitro* test-tube method with purified NO synthase to *in vivo* dosages of agents which inhibit or enhance NO synthase activity in an intact mammal exists in the prior art." (Office Action p. 2). However, again the burden is not on Applicants to provide evidence of

enablement, but is initially on the Examiner to provide evidence showing that persons skilled in the art would reasonably doubt Applicants' asserted utility. In fact, it is well known in the art of pharmaceutics that the results of *in vivo* experimental are frequently used to test pharmaceuticals and that the results from these tests are correlated to predicted results in mammals.

For all of these reasons, it is respectfully submitted that claims 1-15 are sufficiently enabled by the disclosure. New claim 16 directed to a method of regulating or controlling nitric oxide production using the peptide substrates listed on p. 47 is also enabled for the same reasons set forth above. Applicants therefore respectfully request that this ground of rejection be withdrawn.

II. Claim Rejections - 35 U.S.C. § 112, Second Paragraph

Claims 1-15 were rejected under 35 U.S.C. § 112, second paragraph as being indefinite.

The Examiner first states that claims 1, 7, and 10 are indefinite because it is unclear whether the modifier "arginine rich" is intended to modify oligopeptide and protein or only modify peptide. The Examiner further states that "arginine rich" is indefinite because no reference point has been supplied for this term as a point of comparison. While Applicants do not believe this term is indefinite, in the interest of expediting prosecution, claim 1 has now been amended to remove this term and recite that the peptide,

oligopeptide, or protein inhibitor is such that one or more arginine groups are available. Support for this amendment is found on p. 15 of the specification. Claim 7 has been canceled, thereby rendering this ground of rejection moot. Claim 10 does not appear to contain the "arginine rich" language cited by the Examiner.

The Examiner next rejects claims 3, 4, 13, and 14 on the basis that they do not further limit the independent claims. Claims 3 and 13 have now been amended to recite that the peptide, oligopeptide, or protein is selected from the group consisting of L-Arginine, Poly-Arginine, BK, Des-Arg1-BK, Des-Arg9-BK, BK fragment 1-7, BK fragment 2-7, [Lys1]-BK, Lys-BK, Ile-Ser-BK, and Met-Lys-BK. Claims 4 and 14 have been canceled.

Claim 6 was rejected as being inconsistent with independent claim 1. Claim 1 has now been amended to clarify that the peptide, oligopeptide, or protein functions as a substrate for or inhibitor of the nitric oxide synthase, and therefore may be effective in either inhibiting or enhancing NO production. Support for this amendment is found on pp. 28-29 of the specification. Thus, claim 6 can no longer be considered inconsistent.

Claims 7 and 8 were rejected as being unclear as to the meaning of "the nitric oxide synthase of claim 1 or 2." Applicants have now canceled claims 7 and 8, thereby rendering this ground of rejection moot.

Claim 11 was rejected as being unclear. Claim 11 merely notes that the peptide, oligopeptide, or protein acts as a substrate for nNOS-II. It is therefore believed that this claim is not unclear.

Claim 12 was rejected as being unambiguous and unclear. Applicant has now canceled claim 12, thereby rendering this ground of rejection moot.

III. Claim Rejections - 35 U.S.C. § 102

A. Norryd et al.

Claims 1, 2, 5, 6, 10-12, and 15 were rejected under 35 U.S.C. § 102(b) as being anticipated by Norryd et al. The Examiner states that Norryd et al. disclose the administration of bradykinin by injection into an artery. The Examiner argues that while Norryd et al. is silent with regard to the claimed end result of inhibiting nNOS-II, this result is inherent in the one-step method of administering bradykinin.

A rejection for anticipation requires the presence in a single prior art reference disclosure of each and every element of the claimed invention. Lindemann Maschinenfabrik GmbH v. American Hoist & Derrick Co., 730 F.2d 1452, 221 USPQ 481, 485 (Fed. Cir. 1984). Further, the reference must generally place the needed subject matter supporting the anticipation rejection in the public domain before the date of invention. In re Zenitz, 333 F.2d 924, 142 USPQ 158, 160 (C.C.P.A. 1964). It follows from this second element that a reference does not legally anticipate the claimed subject

matter if it is found not to be sufficiently enabling, in other words, if it does not place the subject matter of the claims within the possession of the public. In re Wilder, 429 F.2d 447, 166 USPQ 545 (C.C.P.A. 1970).

Independent claims 1, 10, and 16 set forth Applicants' preferred dosing range of 20-500 μg/kg of arginine-rich peptide, oligopeptide, or protein inhibitor of nitric oxide synthase. Thus, for instance, an 80 kg (~176 lb.) subject would receive a dose of between about 1600-40,000 μg. The inventors have determined that this concentration of peptide, oligopeptide, or protein inhibitor is necessary in order to achieve the claimed effect of regulating or controlling nitric oxide production. (See Specification, p. 36).

Norryd et al. teach the administration of only 5, 10, or 20 μg bradykinin. (Page 119). Thus, Norryd teaches the administration of a dose of bradykinin at least 80 times less than the dose set forth in Applicants' claimed invention. It is therefore respectfully submitted that the method of Norryd does not inherently achieve Applicants' claimed result, and does not place Applicant's invention in the possession of the public. Therefore, claims 1, 2, 5, 6, 10-12, and 15 are not anticipated by Norryd et al.

Claims 1, 2, 5, 6, 10-12, and 15 are also not rendered obvious by Norryd et al. There is no motivation or suggestion in Norryd et al. to increase its dosing amounts of bradykinin by at least 80 times.

B. Groves et al.

Claims 1, 2, 5-12, and 15 were rejected under 35 U.S.C. § 102(b) as being clearly anticipated by Groves et al. Groves teaches the administration of the selective bradykinin B_2 receptor antagonist HOE 140 in order to document its effects on epicardial and resistance vessel function in the human coronary circulation. (Page 3424).

Groves et al. does not teach the administration of from about 20-500 μg/kg of a peptide, oligopeptide, or protein that acts as a substrate for or inhibitor of nitric oxide synthase, whereby the tertiary structure of the peptide, oligopeptide, or protein inhibitor is such that one or more arginine groups are available to the nitric oxide synthase. In fact, Groves et al. teach that the administration of HOE-140 has no effect on NO (see e.g. p. 3429 - "The fact that HOE 140 had no influence on NO synthase activity in cultured endothelial cells implies that its effects were not attributable to a nonspecific inhibition of enzymatic NO formation.") Groves et al. measure the effects of HOE-140 on endothelial cells' ability to produce nitric oxide. They demonstrated that cells treated by HOE 140 versus controls produce the same amounts of nitric oxide. They therefore concluded that the agent has no effect on NO, even though HOE-140 does affect blood pressure (tone) when injected into humans.

In contrast, Applicants are the first to have discovered that arginine-containing peptides, oligopeptides and proteins

act as substrates and inhibitors of NOS. These compounds have been found to bind to NOS and are converted to nitric oxide, and a peptide product containing citrullines. Groves et al. does not place Applicants' claimed invention in the possession of the public, i.e. they do not enable persons skilled in the art to administer arginine-containing peptides, oligopeptides, and proteins and Applicants' claimed dosages in order to control nitric oxide production in mammals. Instead, Groves et al. teach away from the claimed invention in their conclusions that the administration of HOE-140 has no effect on the production of NO. Thus, claims 1, 2, 5-12, and 15 are not anticipated by Groves et al. Claim 16 directed to Applicants' preferred peptide substrates are also not anticipated by Groves et al.

Claims 1, 2, 5-12, 15, and 16 are also not rendered obvious by Groves et al. There is no teaching or suggestion to modify the teachings of Groves et al. to use Applicants' claimed peptides, oligopeptides, and proteins in Applicants' claimed dosing range.

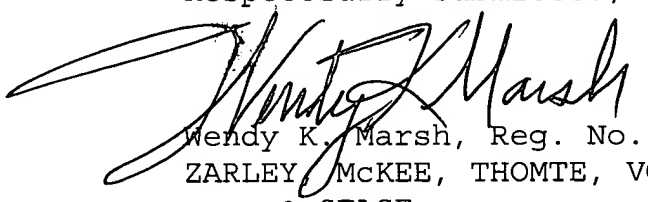
IV. Conclusion

For the above reasons, it is believed that the present application is in a condition for allowability. Allowance is respectfully requested.

Enclosed is a check for $39 for the addition of one independent claim. If this amount is not correct, please

consider this a request to debit or credit Deposit Account No. 26-0084 accordingly.

Respectfully submitted,



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